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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,550	10/31/2003	Susan J. Wong	454311-2232.1	9527

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EXAMINER	
HURT, SHARON L	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,550	WONG ET AL.	
	Examiner	Art Unit	
	Sharon Hurt	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-74,76-105,126-128,145,156 and 162-202* is/are pending in the application.

4a) Of the above claim(s) *69-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74,76-105,126-128,145,156 and 162-202* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the applicant's response received on March 17, 2005. Amended claims were received March 17, 2005. Claims 1-68, 75, 106-125, 129-144, 146-155, and 157-161 have been cancelled. Claims 69-74, 76-80, 89-91, 95, 99, 100, 105, 126-128, 145, and 156 have been amended. New claims 162-202 have been added but have not been previously examined. Claims 69-74, 76-105, 126-128, 145, 156, and 162-202 are pending. Claims 69-73 are withdrawn from further consideration as being drawn to a nonelected invention. Claims 74, 76-105, 126-128, 145, 156, and 162-202 are being examined.

The Patent Examiner for your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Sharon Hurt.

Priority

This application claims benefit to provisional applications 60/422,755, filed on 10/31/2002 and 60/476,513, filed on 06/06/2003. The current application claims a method of detecting West Nile Virus (WNV) infection by testing for NS5 protein. Provisional application 60/422,755 does not disclose the NS5 protein, therefore benefit is denied. The office maintains priority as set out before as benefit to provisional application 60/476,513 only.

Oath/Declaration

The objection to declaration as being defective for not identifying the citizenship of each inventor has been **withdrawn**. A substitute declaration was received and is consistent with the requirements of 37 CFR §1.63 and now indicates the citizenship of each inventor.

Claim Rejections - 35 USC § 101

Claim 105 rejection under 35 USC § 101 has been **withdrawn**. The claim has been amended to include method steps.

Claim Rejections - 35 USC § 112

Claim 75 has been cancelled therefore overcoming all rejections. Rejection to claims 76-78 and 79 has been **withdrawn**. Claims 76-78 and 79 have been amended to overcome the rejection.

The rejection to claims 78, 80 and 90 have been **withdrawn**. Applicant's response has been considered and is persuasive therefore rejection is withdrawn. Claim 80 has been amended to omit "or fragment thereof" therefore overcome the rejection. Claim 90 has been amended to overcome the rejection to "subfragment" therefore the rejection is withdrawn.

The rejection of not setting forth method steps for claim 105 has been **withdrawn**. Claim 105 has been amended to include steps for the claimed method therefore has overcome the rejection.

Claims 126-127, and 145 **stand rejected** under 35 USC §112, second paragraph, as being indefinite in the terminology **"rapidly detecting"** and **"recent infection"**.

The problem with claiming "rapidly detecting" or "recently detecting" is that the claims lack a standard to which the ordinary artisan can make a comparison with. Without any information for comparison the terms are indefinite. "Rapid" the ordinary artisan would understand that it is meant to denote something fast. Fast and rapid are relative terms that require comparison to something that is slow. Here we do not know what to compare the method with thus the term "Rapid" does not add to the claim or the understanding, it is indefinite.

"Recently detecting", it is known in the art that the immune response differs between the first time a person sees an antigen and the reaction to subsequent antigens exposure. Here the claims do not set forth method steps that can differentiate between a recent infection *vs.* an ongoing infection. Thus, the method steps do not correlate back to the preamble and the use of the term in the preamble is thereby indefinite.

The rejections to claims 91, 94 and 126-128 have been **withdrawn**. Claims 91, 94 and 126-128 have been amended to overcome the rejection for the term "**increase reaction kinetics**".

The rejection for claims 74, 80, 91, 99, and 126 **stands** as failing to comply with the enablement requirement. The term **"not substantially or detectably cross-reactive"** fails to define if the anti-WNV antibodies are reactive or not reactive with

antibodies against JEV, SLEV or DENV. The amendments to the claims do not overcome the rejection. The term **"substantially"** is a relative term and the definition fails to clarify if the antibodies are reactive or not reactive. The term "substantially" does not define the metes and bounds of the invention.

The rejection for claims 74, 91, 99 and 126-128 has been **withdrawn**. The claims 74, 91, 99 and 126-128 have been amended to omit "against a flavivirus other than WNV" therefore overcoming the rejection.

The rejection to claims 74 and 80, for reciting "or an immunogenic fragment thereof" has been **withdrawn**. Claims 74, 80, have been amended to delete the phrase "or an immunogenic fragment thereof", therefore overcoming the rejection.

The rejection to claim 156 for the enablement requirement is withdrawn. Claim 156 has been amended to clarify the claimed invention.

The rejection to claim 76 for the enablement requirement is withdrawn. Claim 76 has been amended to clarify the claimed invention.

(*New Rejections*) Claims 171-175, 182-190 and 192-200 are **rejected** under 35 USC §112, second paragraph, as being indefinite in the terminology **"rapidly detecting".** The term "rapidly" and "recent" are relative terms and the bounds of such terms are not known. A comparison for these terms is not provided therefore, the terms are indefinite. The explanation for the use of these terms is provided above.

Claims 163, 168, 177 and 202 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. These claims use the phrase "**in less than about** 3 hours." The term "about" is relative and fails to particularly point out the time the method is performed. The term "in less than" combined with "about" makes the time frame for this method indefinite. The term "about" does not define the metes and bounds of the invention.

Claim Rejections - 35 USC § 103

The rejection of claims 74, 76-82, 85-90 and 126-128 is **withdrawn** in view of applicant's amendments to the claims limiting the reactivity of the cross-reactive antibody to JEV, SLEV or DENV.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74, 76-105, 126-128, 145, 156, and 162-202 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Wang** et al., (Vector Borne and Zoonotic Diseases Vol. 2 Num. 2, 2002, p. 105-109) **Valdes** et al., (Clinical and Diagnostic Laboratory Immunology, Sept 2000 p. 856-857), **Mandy**, F. et al., Clinics in Laboratory Medicine, Vol. 21, p. 713-729), **Scaramozzino** et al.,

(Journal of Clinical Microbiology, May 2001, p. 1922-1927), and US Patent No. 6,416,763 (**McDonell** et al., Jul. 9, 2002).

Applicant argues that in order to establish a case of obviousness over Wang et al. and Valdes et al., there must be a suggestion or motivation to modify the references or to combine the references teachings. Additionally, there must also be a reasonable expectation of success.

Wang teaches a method of detecting WNV infection using a WNV E protein. Wang teaches that recombinant E protein can be used to detect WNV specific antibodies present during infections in humans (p. 106). Wang teaches that using human serum and cerebrospinal fluid from patients can be used to detect WNV from other diseases, including related flaviviral infections. Wang tested sera from horses and humans to confirm WNV infection. Wang mentions that the E protein may be a useful tool to aid in the serological diagnosis of WNV infection in mammals. Wang's WNV E protein was prepared as a recombinant fusion protein with maltose binding protein (p. 106). Wang used secondary antibodies for immunoblots prepared with alkaline phosphatase-conjugated goat anti-horse or anti-human Ig(M and G) (p. 107). The reference does not teach an antibody to detect WNV NS5 protein.

Valdes teaches a method for detecting dengue, a related flavivirus, using dengue E and NS5 antigens. Valdes results confirm that NS3 and NS5 proteins are able to elicit specific antibodies against Dengue virus. The presence of anti-E, -NS3, and -NS5 antibodies in acute-phase samples from primary and

secondary dengue cases suggests the possibility of implementing new diagnostic assays with higher sensitivity for E, NS3, and NS5 antigen detection that allow the early diagnosis of dengue fever and dengue hemorrhagic fever (p. 857). The reference does not teach detecting WNV NS5 protein.

Mandy teaches that functional modules for the suspension array technology (SAT) are the same as for radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) (p. 713). Mandy teaches a microsphere coupled to a bead and also teaches a second antibody as a reporter (p. 714-715). Mandy teaches that SAT can be constructed as a direct or an indirect method depending upon the nature of the attachment of the fluorochromes to the reporter molecules. Mandy refers to reaction kinetics as the quality of monoclonal antibodies, the level of sensitivity required, the level of suspension agitation available, and selected temperature all contribute to the duration of the incubation, with anticipated time for incubations ranges from 15 to 2 hours (p. 725). Mandy teaches that the techniques are applicable to biological samples such as bodily fluids and whole blood in volumes as small as 10-20 microliters (p. 724).

Mandy teaches that antibodies that are used in ELISA assays can predictably be used in SAT assays. The function of the antibody, which is to bind antigens, is a feature of the antibody that does not change with the change in assay format. The reference teaches antibodies can be used in SAT format. The reference does not teach an anti NS5 WNV antibody.

Scaramozzino teaches the detection of flavivirus by PCR using NS5 gene sequences. Scaramozzino compared different flaviviruses (both mosquito- and tick-transmitted) with RT-PCR assays. Scaramozzino teaches a new heminested PCR using different NS5 locations (ranging from 9006 to 9258). The fragments of the expected 250-bp target size were successfully amplified from all mosquito- and tick-transmitted flaviviruses tested. Results designed on the basis of the NS5 gene was the only pair able to detect all targeted viruses, and there was no problem of specificity towards other tested viruses. Using these primers, detection of flavivirus can be used by electrophoresis on an agarose gel or a more sensitive technique, ELISA, or revelation of amplified products stained by digoxigen. Using the heminested products in the NS5 location (220 bp) allowed the detection of flaviviruses; DEN, JE, YF, TBE and WN groups in patients samples. Serum and cerebrospinal fluid samples from patients were tested with sequencing and comparison of the NS5 amplified products classified the viruses among WN species. The identification was confirmed by a species-specific PCR targeting the envelope gene of WN viruses. This PCR screening procedure could be used as a first-line diagnostic PCR screening test for an unknown virus to characterize viruses to the pathogenic members of genus *Flavivirus*. It would take only a few hours by using PCR to directly detect a flavivirus from a patient sample and the PCR amplification in real time allows a quicker diagnosis.

Scaramozzino et al. teaches that at the time the invention was made it was known in the art that NS5 sequence between related flaviviruses differ

enough to allow NS5 to be used as a diagnostic tool. The reference uses a PCR amplification and sequences to make the differential diagnosis.

The ordinary artisan would have known that these sequence differences among the NS5 protein can be exploited for diagnosis. The reference does not teach a NS5 WNV antibody.

McDonnell teaches an immunogenic composition containing a recombinantly produced nonstructural (NS) protein and a second recombinantly produced flavivirus truncated envelope (E) protein. This immunogenic composition can be used in an acceptable carrier as a pharmaceutical composition, vaccine, and as an immunodiagnostic for the detection of flavivirus. McDonnell teaches the flavivirus NS proteins may include NS1, NS2, NS3, NS4 and NS5. McDonnell's invention relates to the use of compositions with flavivirus E protein in combination with NS proteins as immunogenic antigens that stimulate as immunological response in a host subject by eliciting antibody formation and/or cellular immune response. Antigens can be used in immunoassays to detect antibody levels and antibodies to protein within biological samples, including blood and serum samples, can be detected. Immunoassay protocols may be based upon competition, or direct reaction, or sandwich type assays. Most assays involve the use of labeled antibody or polypeptide; the labels may be fluorescent, chemiluminescent, radioactive, or dye molecules. Assays which amplify the signals from the probe are also known; examples of which are assays that utilize biotin and avidin, and enzyme-labeled

and mediated immunoassays, such as ELISA assays. Kits suitable for immunodiagnosis and containing the appropriate labeled reagents are constructed by packaging the appropriate materials, including the compositions of the invention, in suitable containers along with the remaining reagents and materials (for example, suitable buffers, salt solutions, etc.) required to conduct the assay, as well as suitable set of assay instructions.

In summary, Wang teaches the WNV E protein is specific for detecting WNV in patient samples. Valdes teaches a method to detect DENV with higher sensitivity using NS5 proteins. Mandy teaches SAT technology, RIA, ELISA , microsphere coupled reactions and attachment of the fluorochromes to detect antibodies in biological samples. Scaramozzino teaches the detection of flavivirus by PCR with NS5 gene sequences. Scaramozzino teaches a new heminested PCR using different NS5 locations allowing the specific detection of DEN, JE, YF, and WN from patient samples. McDonnell teaches an immunogenic composition containing a recombinant NS protein and a second recombinant flavivirus E protein. This composition with NS proteins has immunogenic antigens that can be used to detect flavivirus infections. Methods of use include fluorescent antibody labeling and ELISA for diagnostic assays and kits containing the assay products and instructions.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teaching of Wang, Valdes and Mandy to use WNV NS5 protein to detect WNV infections in humans and horses.

A person of ordinary skill in the art would have been motivated to use the NS5 and E proteins as immunodiagnostic assays for the detection of WNV in biological samples. McDonnell teaches a diagnostic kit with an immunogenic composition using ELISA and fluorescent labeling.

One would have expected success because of the teachings of Scaramozzino who developed a rapid, sensitive PCR assay for the detection of flavivirus with NS5 gene sequences. These references combined teach the limitations of the claims.

Double Patenting

The rejection of claims 74, 76-105, 126-128, 145, 156, and 162-202 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-9, 13-21, 24-35 and 56-57 of copending Application No. 10/839,442 is maintained. Although the conflicting claims are not identical, they are not patently distinct from each other because both sets of claims are directed to a method of detecting WNV infection in a subject using flavivirus molecules with specificity towards NS5. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

New rejections in view of applicant's amendments to the claims:

Claim rejections under 35 USC §112, second paragraph as being indefinite in the terminology.

Claim rejections under 35 U.S.C. 103(a) as being unpatentable over Wang et al., Valdes et al., Mandy et al., Scaramozzino et al., and McDonell et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Hurt whose telephone number is 571-272-3334. The examiner can normally be reached on M-F 8:00 - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Housel James can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 13, 2006

James C. Housel 2/20/06

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